A Review Paper

Contemporary Alternatives to Synthetic Bone Grafts for Spine Surgery

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Abstract

The goal in performing spinal fusion techniques is to achieve solid fusion, which will maximize clinical outcomes. This goal has generated enormous interest in developing bone graft alternatives or extenders that enhance or replace autologous bone graft.

Autogenous bone graft from the iliac crest is still the gold standard for graft materials because it has all 3 properties essential for adequate fusion. The search for a synthetic graft as good as or better than iliac crest bone graft has recently intensified with the emphasis on minimizing the invasiveness of surgical techniques, including harvest of iliac crest autograft (such harvesting can be associated with significant donor site morbidity).

Increasingly being studied are biologically active substances intended to extend, enhance, or even replace autologous graft. These substances include (a) allograft cancellous chips and (b) cortical spacers that are both osteoconductive (provide bone scaffold) and weakly osteoinductive (promote new bone formation), including demineralized bone matrix products. Human recombinant bone morphogenetic proteins (BMPs), including recombinant human BMP-2 (rhBMP-2) and recombinant human osteogenic protein 1 (rhOP-1 or rhBMP-7), are being investigated in human clinical trials and show promise as autologous bone graft substitutes.

Synthetic bone grafts (ceramics), such as hydroxyapatite and β-tricalcium phosphate, provide scaffolds similar to those of autologous bone, are plentiful and inexpensive, and are not associated with donor morbidity. Furthermore, adding silicon may increase the bioactivity of calcium phosphate and enhance interactions at the graft–host interface.

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Augmentation of internal fixation in spinal fusion surgery with autogenous or allogeneic bone graft or bone graft substitutes is the sine qua non step in inducing successful fusion in modern spinal surgery. Absence of osteoconductive, osteoinductive, and biological factors creates a hostile setting for osteogenesis, whereas presence of such substances, in varying amounts and in conjunction with stability, creates a favorable mechanical and biological environment for the successful formation of new bone.[1-4]

Nevertheless, debate over which materials and techniques result in the highest rates of successful fusion at the lowest morbidity to the patient and cost to society is heated. According to data collected by the American Academy of Orthopaedic Surgeons, more than 500,000 bone graft procedures are performed annually in the United States. Of these procedures, slightly less than half are performed as an adjunct to spinal fusion surgery.[5] Therefore, given their great popularity and potentially large impact on spinal surgery outcomes, bone graft materials and biology have become a formidable topic of research.

Synthetic Alternatives

Bone biosynthesis requires cells (eg, osteoblasts), growth factors (eg, bone morphogenetic proteins [BMPs]), and an appropriate scaffold. Use of human bone tissue, either whole or as a constituent of a composite graft (eg, demineralized bone matrix [DBM]), provides one or more of these components naturally. Synthetic bone graft substitutes are materials that can provide the necessary components for osteogenesis but that do not occur naturally. They are formed from materials that may have chemical and biological properties similar to those of real bone but that offer other benefits, such as no or very low antigenicity, abundant supply, suitable and predictable mechanical properties, ease of use, and very low risk of spreading disease.

Ceramic-based synthetic bone grafts capitalize on the chemical composition of the inorganic phase of natural bone as a scaffold for new bone production. For example, hydroxyapatite (HA) has 2 properties that make it attractive as a bone graft substitute. First, it can be formed into a 3-dimensional structure that is rigid and stable. Stability is conducive to new bone formation because it allows for ingrowth of bone elements (collagen and inorganic elements) as well as nutrient blood vessels (angiogenesis). Second, at the macroscopic level, the building blocks of HA can be organized to form micropores of ideal size for osteogenesis and angiogenesis. Pore diameter and the degree to which pores communicate (interconnectivity)

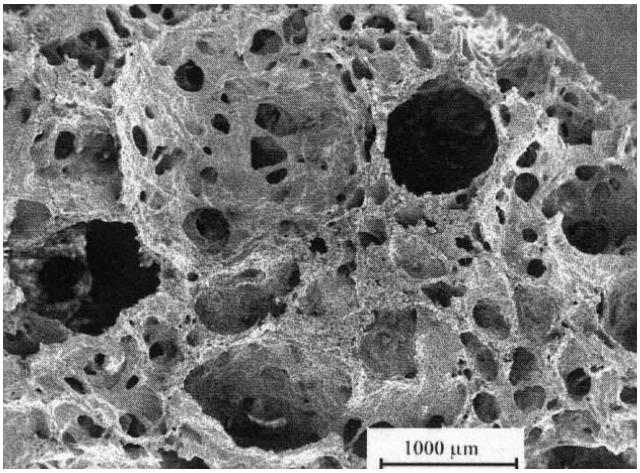

Figure 1. Electron microscopy of Vitoss™ (Orthovita, Malvern, Pa) 3-dimensional shape. Image courtesy of Orthovita.

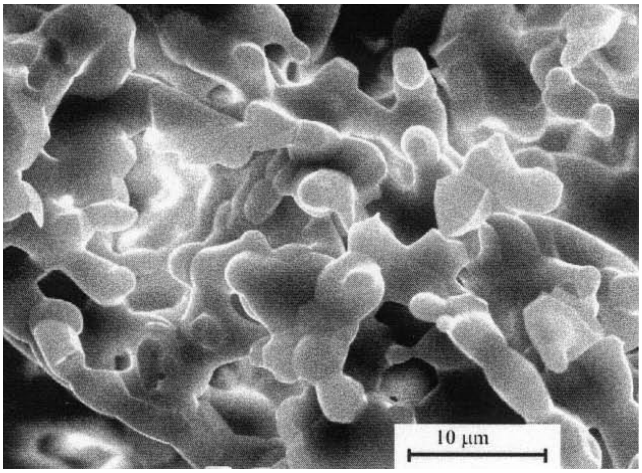

Figure 2. Electron microscopy of Vitoss with new bone formation. Image courtesy of Orthovita.

are the major determinants of the speed with which a graft will be incorporated and remodeled. Optimal pore size for osteoconduction is 150 to 500 micrometers[6]; larger pores reduce stress shielding at the microscopic level, whereas smaller pores have a role in transporting fluids containing nutrients and oxygen through the scaffold.[7]

When implanted graft materials fail, they fail at the interface between the implanted material and the host tissue.[8] It is suggested that the more biocompatible an implant is at its surface, the more efficiently it will be incorporated into new bone formation and the less likely the construct will fail. This is the rationale behind ceramic (HA)–based synthetic bone grafts; as bone in its inorganic phase is also composed of HA, the bone–graft interface allows for rapid incorporation of new bone. Furthermore, the porosity incorporated into HA provides the essential scaffold design for proper bone ingrowth, thus creating a stable interface for new bone formation.

HA-based synthetic grafts have been used with varying degrees of success. Pro Osteon® (Biomet Spine, Parsippany, NJ) is a commercially available ceramic graft derived from sea coral. Sea coral consists primarily of calcium carbonate, which can be chemically transformed fully or partially into HA during manufacturing. Depending on the duration of the reaction cycle, the scaffold consists either of a thin layer of HA over a calcium carbonate scaffold (resorbable in 6-18 months) or a fully reacted HA scaffold (slowly resorbing at 2%-5% per year). In addition, specific coral species can be selected to create implants with different pore sizes, thus emulating either cortical or cancellous bone. Thalgott and colleagues[9] reported using Pro Osteon 200 (pore diameter, 200 micrometers) in combination with rigid plating after anterior cervical decompression and fusion of 26 patients. The reported fusion rate after a minimum of 2 years of follow-up was 100%, with mean decrease in overall pain of 76%. In a separate study of anterior cervical interbody fusion with plating using Pro Osteon 200, McConnell and colleagues[10] reported clinical improvement comparable to that attained with autologous iliac crest bone graft. Several other clinical studies have found Pro Osteon 200 fusion rates of 93% to 100% and patient satisfaction rates of approximately 90%.[11] Pro Osteon 500 (pore diameter, 500 micrometers) closely resembles cancellous bone in structure but has only 25% of the compressive strength of Pro Osteon 200. Pro Osteon 500 has shown effectiveness as a graft extender in instrumented posterolateral lumbar fusion procedures.[12]

The synthetic bone graft alternatives most commonly used are made from β-tricalcium phosphate (β-TCP).[9] These substances are chemically similar to normal bone and thus have very low immunologic reaction levels. β-TCP resorption occurs through both phagocytosis (macrophages) and chemical dissolution. The rate at which phagocytosis occurs depends on the rate of particulate debris generation by chemical dissolution. When particulate debris is generated in excess, a full-fledged inflammatory reaction can occur, leading to loss of ingrowing bone and fibrous tissue encapsulation. These processes create a local environment rich in osteogenic substrates to be used by activated osteoblasts. Scaffolds made of mixtures of HA and β-TCP provide osteoconduction for bone production as well as long-term stability, leading to successful incorporation of a bone-fusion mass.[13,14] Over time, the stable tertiary structure of the HA portion of the graft does not resorb, imparting structural rigidity to the fusion site while the β-TCP is resorbed.

Vitoss™ (Orthovita, Malvern, Pa) is a commercially available highly porous β-TCP ceramic bone graft alternative (Figure 1).[15] Vitoss is marketed as a bone graft substitute with 90% open, interconnected porosity, resembling the multidirectional interconnected porosity of human cancellous bone.[16] Pore sizes range from 1 to 1000 micrometers; larger pores allow for cell seeding, migration, and bony ingrowth, whereas smaller pores encourage neovascularization and allow for the capillary transport of vital nutrients and oxygen to osteoblasts and osteoclasts seeded throughout the scaffold.[12] Vitoss resorption as part of bone formation and remodeling yields a variety

of bone-forming substrates, such as minerals (Figure 2). Exogenous cells and a variety of cytokines may be delivered to a ceramic scaffold through a bone-marrow aspirate to be used as a composite graft. In a prospective study of 50 patients undergoing posterior lumbar spinal fusion through bilateral posterolateral intertransverse fusion (PLITF) after decompressive laminectomy, Vitoss, in conjunction with autograft (either iliac crest graft or locally harvested), demonstrated 100% radiographic evidence of bone formation at 5 to 7 months among the 32 patients who were successfully followed up.[17] Use of iliac crest bone was completely avoided in 14% of patients, and a mean of 30% less iliac crest bone was required from patients who underwent iliac crest bone harvest. A separate study of 7 patients who underwent anterior lumbar (ALIF) or posterior lumbar (PLIF) interbody fusion (12 levels total) demonstrated 100% radiographic fusion at both 3-month and 6-month follow-up, with no evidence of allograft subsidence, extrusion, fracture, or resorption when Vitoss was mixed with venous blood, without autograft, and used within a femoral ring allograft.[18] Thus, there is evidence supporting use of β-TCP combined with venous blood or bone-marrow aspirates as a substitute for actual cancellous autograft, though there may be concerns about its use in patients in whom, for metabolic or other reasons, graft dissolution occurs before there is sufficient osteoconduction.

Processed ceramic scaffolds may also be combined with weakly osteoinductive processed allograft bone matrices to enhance graft or fusion healing. Allomatrix™ (Wright Medical Technology, Memphis, Tenn) combines the osteoinductive and osteoconductive properties of DBM with calcium sulfate to form an injectable putty. Wilkins and Kelly[19] reported on their use of Allomatrix in 76 patients who had long-bone defects caused by either fracture nonunion or benign tumor. Of these patients, 97% received Allomatrix injection alone, and 3% received Allomatrix with bone-marrow aspirate. At a mean follow-up of 7 months, 85.1% of the nonunion patients and 93% of the benign tumor patients showed radiographic evidence of fusion.

Silicon-Containing Synthetic Grafts

Scientists continue to try to enhance the biological response to synthetic bone graft materials through a variety of means. The latest synthetic bone graft materials explore the role of silicon in bone biosynthesis. The effects of silicon on bone biosynthesis have been studied since the 1960s. In 1970, Carlisle[20] demonstrated, through electron probe microscopy, that silicon has a role in bone formation, given its presence in the active calcification sites of young mouse and rat bones. She further demonstrated that the amount of silicon present was related to the maturity of the bone mineral. Both calcium and silicon content were noted to increase during bone development, while silicon content leveled off at the time of bone maturity. In 1972, Carlisle[21] and Schwartz and Milne[22] demonstrated that baby chickens fed diets deficient in silicon had low levels of collagen in their bones, poor bone development, and many bony malformations. Furthermore, rats that were fed a calcium-deficient diet and supplemented with silicon still demonstrated sufficient calcification and increased bone mass after 3 weeks. In later studies, rats fed silicon-deficient diets were found to have decreased levels of acid and alkaline phosphatase activities in their femurs, compared with rats fed adequate amounts of silicon.[23-25] Silicon-deficient rats also demonstrated decreased activity of plasma ornithine aminotransferase, a key enzyme in collagen biosynthesis.[26]

Silicon deficiency also leads to decreased levels of copper, phosphorous, manganese, calcium, and magnesium and increased levels of iron in various bones across multiple animal species.[27-29] In certain animal models, a correlation has been noted between decreased dietary silicon and decreased collagen and copper concentrations.[30] As dietary supplementation with silicon increases, so does the concentration of copper in bone. Copper is known to have a role in cross-linking collagen fibrils, and silicon seems to affect the functioning of the key enzyme prolyl hydroxylase, a fundamental enzyme in the extracellular cross-linking of collagen fibrils needed to form the mature type 1 collagen fibers seen in bone. In addition, there are reports that soluble silicon released locally induces osteogenic differentiation and stimulation of osteoblasts to form new bone.[28] Reffitt and colleagues[28] demonstrated that orthosilic acid (endogenous human substrate that contains soluble silicon) in physiologic concentrations (5-20 micrograms) stimulated collagen type 1 synthesis and enhanced osteoblast differentiation. Xynos and colleagues[29] and Gao and colleagues[32] demonstrated the upregulation of several genes expressed by osteoblasts, including the gene for BMP-2, when exposed to the ionic products of resorbable bioactive glasses ($CaO–P_2O_5–SiO_2–Na_2O$).

Incorporation of silicon may increase the bioactivity of calcium phosphate ceramic materials locally, both by enhancing interactions at the graft–host interface and by having a potential paracrine-like effect on host osteoblasts. Therefore, silicate-substituted calcium phosphate materials, in which silicate groups selectively replace a portion of the phosphate groups within the chemical lattice structure, may have improved bone grafting qualities. These newer products combine the optimal osteoconductive properties of HA with the augmented bioactive properties of silicon. Silicon addition augments the bioactive properties of calcium phosphates and potentially provides a catalyst for bone formation local to the implant surfaces. There are reports of successful osteoblast growth on silicon nitride ceramics.[33]

Actifuse™ Synthetic Bone Graft (ApaTech Inc, Foxborough, Mass) was recently introduced to the US market. In Actifuse, silicate groups selectively replace phosphate groups in the calcium phosphate lattice structure. Unlike earlier glass and glass-ceramic bone substitutes, which contained enough silicon ultimately to cause cell death, Actifuse contains 0.8% silicon by weight, which has been shown to optimize the osteogenic response in the distal femur in rabbits.[31,34] In this model, this unique chemistry, in combination with a 3-dimensional structure containing interconnected macroporosity and microporos-

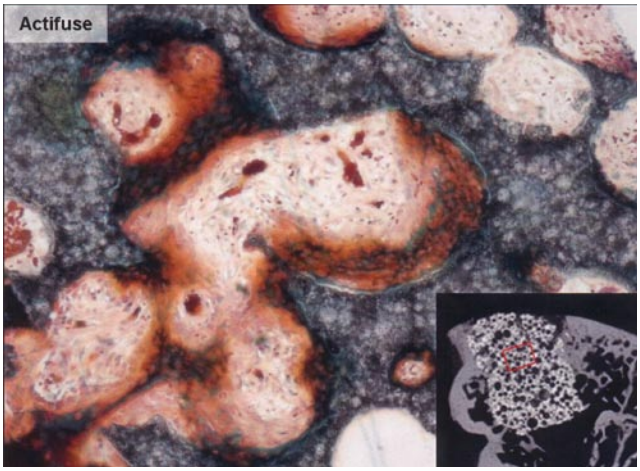

Figure 3. Bone formation in the center of a 6-mm-deep X 4.5-mm-diameter cylinder of Actifuse™ Synthetic Bone Graft (ApaTech Inc, Foxborough, Mass) implanted longitudinally in a rabbit distal femur. At only 1 week, there is capillary penetration throughout the porous structure. Although woven bone penetrated through the periphery of the implant to a depth of 0.5 to 1.0 mm, evidence of direct bone formation and mineralization is apparent in the center of the implant. Image courtesy of Apatech.

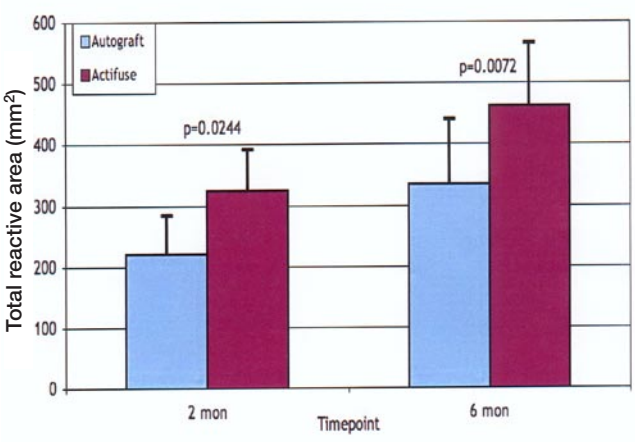

Figure 4. Total reactive area (fusion mass) for autograft and Actifuse determined by histomorphometry at 2 and 6 months in a sheep posterolateral instrumented spine fusion model. Actifuse has more fusion mass than autograft at both time points ($P<.05$). Values are means and SDs. Reprinted from *The Spine Journal,* Volume 7(3), Wheeler DL, Jenis LG, Kovach ME, Marini J, Turner AS. Efficacy of silicated calcium phosphate graft in posterolateral lumbar fusion in sheep, pages 308-317, Copyright 2007, with permission from Elsevier.

ity, creates an "osteogenic catalyst" that promotes rapid bone formation and an elevated volume of bone ingrowth compared with traditional calcium phosphates of similar structure. As with other ceramic materials, bone-marrow aspirate containing autogenous cells and cytokines may be physically combined with porous granules to form a composite graft. Early clinical experience using the product in spinal fusion is encouraging (Figures 3-5).

Composite Grafts

Synthetic grafting materials are now routinely combined with various active biological substances to enhance their osteogenic potential. The synthetic grafting material provides some osteoconductivity; when organic material is added, there is a biological synergistic effect resulting in promotion of new bone formation. One such product, HEALOS® (DePuy Spine, Raynham, Mass), combines autogenous bone-marrow aspirate with HA-coated cross-linked type 1 collagen fibrils. The bone-marrow aspirate provides osteoprogenitor cells and substrate, and the HA-coated collagen matrix forms an environment suitable for immediate remodeling into new bone. Other composite grafts include porous ceramics coated with mesenchymal stem cells; biphasic ceramic (60% HA, 40% β-TCP) combined with bovine type 1 collagen fibers (Collagraft™; NeuColl Corporation, Los Gatos, Calif); absorbable collagen sponges coated with recombinant human BMP (rhBMP); and biodegradable polymers used as delivery systems for rhBMPs (ie, polytetrafluoroethylene, polylactic acid, polyglycolic acid).

Conclusions

Although it is universally agreed that bone graft, in some form, has a vital role in facilitating bony fusion in spinal fusion surgery, bone-grafting methods and materials are

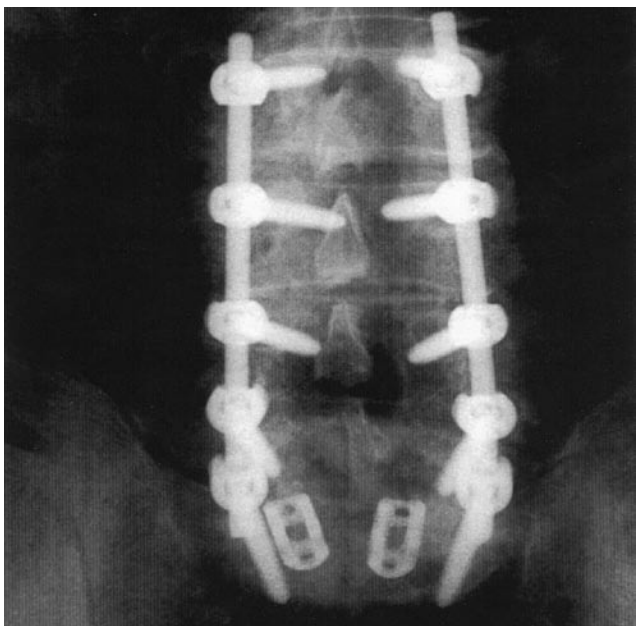

Figure 5. Anteroposterior x-ray obtained 6 months after surgery shows Actifuse in the lateral gutter of this multilevel posterolateral instrumented lumbar fusion. The granular nature of Actifuse is no longer evident, and the synthetic bone graft is integrated into the fusion mass. Of particular note, the margins of the visible fusion mass are smoothly contoured, which may correspond to formation of a pseudocortex.

extremely diverse. Use of an adequate amount of autograft bone has been the most reliable route to successful fusion, though results have remained unpredictable, and the morbidity associated with graft harvest is well established and often dampens otherwise positive clinical results. Furthermore, each bone graft alternative has its advantages and disadvan-

tages. The introduction of silicon-augmented synthetic bone grafts and of newer composite grafts is extremely exciting and brings us closer to the ultimate goal of finding the perfect bone graft alternative, one that promises a more effective treatment and a more predictable outcome for patients requiring spinal fusion.

Authors' Disclosure Statement

Dr. Brandoff and Dr. Silber report no actual or potential conflict of interest in relation to this article.

Dr. Vaccaro wishes to note that he was a paid consultant in the past for Apatech, and he is a stockholder with Orthovita.

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